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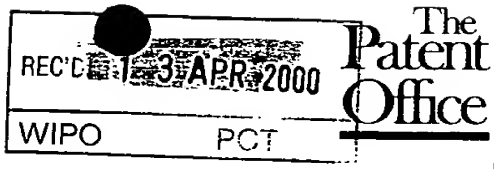

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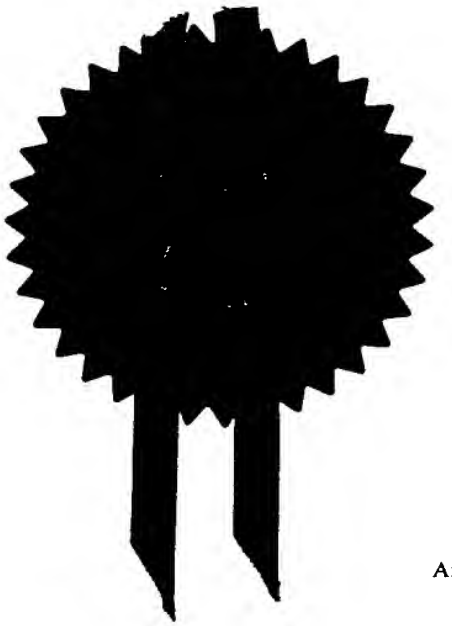

Signed A M Brewer

Dated 6 April 2000

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(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
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1. Your reference — REP06060GB

2. Patent application number *(The Patent Office will fill in this part)* — **9906585.6** — 22 MAR 1999

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Darwin Discovery Limited
Cambridge Science Park
Milton Road
Cambridge
CB4 4WE
United Kingdom

Patents ADP number *(if you know it)* 74240540001

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

4. Title of the invention — HYDROXAMIC AND CARBOXYLIC ACID DERIVATIVES

5. Name of your agent *(if you have one)* — GILL JENNINGS & EVERY

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Broadgate House
7 Eldon Street
London
EC2M 7LH

Patents ADP number *(if you know it)* — 745002

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

YES

Patents Form 1/77

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Continuation sheets of this form	
Description	12
Claim(s)	3
Abstract	
Drawing(s)	

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. For the Applicant
Gill Jennings & Every

I/We request the grant of a patent on the basis of this application.

Signature

Date 22 March 1999

12. Name and daytime telephone number of person to contact in the United Kingdom

PERRY, Robert Edward
0171 377 1377

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HYDROXAMIC AND CARBOXYLIC ACID DERIVATIVES

Field of the Invention

This invention relates to hydroxamic and carboxylic acid derivatives, and to their use in medicine.

Background to the Invention

Metalloproteinases, including matrix metalloproteinase (MMP), (human fibroblast) collagenase, gelatinase and TNFα convertase (TACE), and their modes of action, and also inhibitors thereof and their clinical effects, are described in WO-A-9611209, WO-A-9712902 and WO-A-9719075, the contents of which are incorporated herein by reference. MMP inhibitors may also be useful in the inhibition of other mammalian metalloproteinases such as the adamalysin family (or ADAMs) whose members include TNFα convertase (TACE) and ADAM-10, which can cause the release of TNFα from cells, and others, which have been demonstrated to be expressed by human articular cartilage cells and also involved in the destruction of myelin basic protein, a phenomenon associated with multiple sclerosis.

Compounds which have the property of inhibiting the action of metalloproteinases involved in connective tissue breakdown, such as collagenase, stromelysin and gelatinase, have been shown to inhibit the release of TNFα both *in vitro* and *in vivo*. See Gearing *et al* (1994), Nature 370:555-557; McGeehan *et al* (1994), Nature 370:558-561; GB-A-2268934; and WO-A-9320047. All of these reported inhibitors contain a hydroxamic acid zinc-binding group, as do the imidazole-substituted compounds disclosed in WO-A-9523790. Other compounds that inhibit MMP and/or TNFα are described in WO-A-9513289, WO-A-9611209, WO-A-96035687, WO-A-96035711, WO-A-96035712 and WO-A-96035714.

Summary of the Invention

The invention encompasses novel compounds of formula (I) which are useful inhibitors of matrix metalloproteinases and/or TNFα mediated diseases, including degenerative diseases and certain cancers.

Novel compounds according to the invention are of the general type represented by formula (I):

$(B)_2N\text{-}X\text{-}(CH_2)_m\text{-}W\text{-}(CR^1R^2)_n\text{-}COY$ (I)

wherein

n = 0-1;

m = 0-1;

X is $S(O)_{1-2}$;

Y is OH or NHOH;

W is aryl or heteroaryl;

R^1 is H or a group (optionally substituted with R^3) selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, C_{1-6} alkyl-aryl, heteroaryl, C_{1-6} alkyl-heteroaryl, cycloalkyl, C_{1-6} alkyl-cycloalkyl, heterocycloalkyl, C_{1-6} alkyl-heterocycloalkyl; and

R^2 is H or C_{1-6} alkyl;

or CR^1R^2 is cycloalkyl or heterocycloalkyl optionally substituted with R^3 or a group (optionally substituted with R^3) selected from C_{1-6} alkyl, aryl, C_{1-6} alkyl-aryl, heteroaryl, C_{1-6} alkyl-heteroaryl;

R^3 is OR^7, COR^7, CO_2R^6, $CON(R^7)_2$, $N(R^7)_2$ NR^7COR^7, $NR^7CON(R^7)_2$, $NR^7CO_2R^8$, $NR^7SO_2R^8$, $S(O)_{0-2}R^8$, $SO_2N(R^7)_2$ or cycloimidyl (optionally substituted with R^4);

R^4 is C_{1-6} alkyl;

B is H or a group (optionally substituted with R^5) selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, C_{1-6} alkyl-aryl, heteroaryl, C_{1-6} alkyl-heteroaryl, cycloalkyl, C_{1-6} alkyl-cycloalkyl, heterocycloalkyl, C_{1-6} alkyl-heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl; and each instance of B may be the same or different;

R^5 is H, R^6 or a group (optionally substituted with R^6) selected from C_{1-6} alkyl, aryl, C_{1-6} alkyl-aryl, heteroaryl, C_{1-6} alkyl-heteroaryl, cycloalkyl, C_{1-6} alkyl-cycloalkyl, heterocycloalkyl, C_{1-6} alkyl-heterocycloalkyl,

or B-N-B is heterocycloalkyl optionally substituted with R^5 or $=NOR^5$;

R^6 is H or a group selected from $N(R^7)_2$ NR^7COR^7, $NR^7CON(R^7)_2$, $NR^7CO_2R^8$, $NR^7SO_2R^8$, OR^7, COR^7, CO_2R^4, $CON(R^7)_2$, $S(O)_{0-2}R^8$, or $SO_2N(R^7)_2$;

R^7 is H or a group selected from C_{1-6} alkyl, aryl, C_{1-6} alkyl-aryl, heteroaryl, C_{1-6} alkyl-heteroaryl, cycloalkyl, C_{1-6} alkyl-cycloalkyl, heterocycloalkyl and C_{1-6} alkyl-heterocycloalkyl, wherein said group is optionally substituted with R^8, COR^8, $SO_{0-2}R^8$,

CO_2R^8, OR^8, $CONR^4R^8$, NR^4R^8, or $SO_2NR^4R^8$ and for each case of $N(R^7)_2$ the R^7 groups are the same or different or $N(R^7)_2$ is heterocycloalkyl optionally substituted with R^8, COR^8, $SO_{0-2}R^8$, CO_2R^8, OR^8, $CONR^4R^8$, NR^6R^8, or $SO_2NR^4R^8$;

R^8 is C_{1-6} alkyl, aryl, C_{1-6} alkyl-aryl, heteroaryl or C_{1-6} alkyl-heteroaryl;

and the salts, solvates, hydrates, N-oxides, protected amino, protected carboxy and protected hydroxamic acid derivatives thereof.

Combinations of substituents and/or variables are only permissible if such combinations result in stable compounds.

Description of the Invention

Preferred compounds of the invention are those wherein any one or more of the following apply:

X is SO_2

Y is NHOH

B-N-B is optionally substituted heterocycloalkyl

It will be appreciated that the compounds according to the invention can contain one or more asymmetrically substituted carbon atoms. The presence of one or more of these asymmetric centres in a compound of formula (I) can give rise to stereoisomers, and in each case the invention is to be understood to extend to all such stereoisomers, including enantiomers and diastereomers, and mixtures including racemic mixtures thereof.

It will further be appreciated that the compounds according to the invention may contain an oxime. This oxime can give rise to geometrical isomers, and in each case the invention is to be understood to extend to all such isomers and mixtures thereof.

As used in this specification, alone or in combination, the term "C_{1-6} alkyl" refers to straight or branched chain alkyl moiety having from one to six carbon atoms, including for example, methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, pentyl, hexyl and the like.

The term "C_{2-6} alkenyl" refers to a straight or branched chain alkyl moiety having two to six carbon atoms and having in addition one double bond, of either E or Z stereochemistry where applicable. This term would include for example, vinyl, 1-propenyl, 1- and 2- butenyl, 2- methyl-2-propenyl etc.

The term "C_{2-6} alkynyl" refers to a straight or branched chain alkyl moiety having two to six carbon atoms and having in addition one triple bond. This term would include for example, ethynyl, 1-propynyl, 1- and 2- butynyl, 1- methyl-2-butynyl etc.

The term "cycloalkyl" refers to a saturated alicyclic moiety having from three six carbon atoms and includes for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

The term "heterocycloalkyl" refers to a saturated heterocyclic moiety having from two to six carbon atoms and one or more heteroatom from the group N, O, S (or oxidised versions thereof) which may be optionally benzofused at any available position. This includes for example azetidinyl, pyrrolidinyl, tetrahydrofuranyl, piperidinyl, benzodioxole and the like.

The term "aryl" refers to an aromatic carbocyclic radical having a single ring or two condensed rings, optionally substituted with an aryl group substituent. This term includes, for example phenyl or naphthyl.

The term "heteroaryl" refers to aromatic ring systems of five to ten atoms of which at least one atom is selected from O, N and S, and optionally substituted with an aryl group substituent. This term includes for example furanyl, thiophenyl, pyridyl, indolyl, quinolyl and the like.

The term "aryl group substituent" refers to a substituent chosen from halogen, CN, CF_3, CHF_2, CH_2F, and NO_2.

The term "halogen" means fluorine, chlorine, bromine or iodine.

The term "benzofused" refers to the addition of a benzene ring sharing a common bond with the defined ring system.

The term "cycloimidyl" refers to a saturated ring of five to ten atoms containing the atom sequence -C(=O)NC(=O)-. The ring may be optionally benzofused at any available position. Examples include succinimidoyl, phthalimidoyl and hydantoinyl.

The term "optionally substituted" means optionally susbsituted with one or more of the groups specified, at any available position or positions.

The terms "protected amino", "protected carboxy" and "protected hydroxamic acid" mean amino, carboxy and hydroxamic acid groups which can be protected in a manner familiar to those skilled in the art. For example, an amino group can be protected by a benzyloxycarbonyl, *tert*-butoxycarbonyl, acetyl or like group, or may be in the form of a phthalimido or like group. A carboxyl group can be protected in the form of a readily-cleavable ester such as the methyl, ethyl, benzyl or *tert*-butyl ester. A

hydroxamic acid may be protected as either N or O-substitued derivatives, such as O-benzyl or O-*tert*-butyldimethylsilyl.

Salts of compounds of formula (I) include pharmaceutically-acceptable salts, for example acid addition salts derived from inorganic or organic acids, such as hydrochlorides, hydrobromides, p-toluenesulphonates, phosphates, sulphates, perchlorates, acetates, trifluoroacetates, propionates, citrates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

Salts may also be formed with bases. Such salts include salts derived from inorganic or organic bases, for example alkali metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

When the "protected carboxy" group in compounds of the invention is an esterified carboxyl group, it may be a metabolically-labile ester of formula CO_2R^9 where R^9 may be an ethyl, benzyl, phenethyl, phenylpropyl, α or β naphthyl, 2,4-dimethylphenyl, 4-*tert*-butylphenyl, 2,2,2-trifluoroethyl, 1-(benzyloxy)benzyl, 1-(benzyloxy)ethyl, 2-methyl-1-propionyloxypropyl, 2,4,6-trimethylbenzyloxymethyl or pivaloylmethyl group.

Compounds of the general formula (I) may be prepared by any suitable method known in the art and/or by the following processes.

It will be appreciated that, where a particular stereoisomer of formula (I) is required, the synthetic processes described herein may be used with the appropriate homochiral starting material and/or isomers maybe resolved from mixtures using conventional separation techniques (e.g. HPLC).

The compounds according to the invention may be prepared by the following process. In the description and formulae below the groups R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, W, B, X and Y are as defined above, except where otherwise indicated. It will be appreciated that functional groups, such as amino, hydroxyl or carboxyl groups, present in the various compounds described below, and which it is desired to retain, may need to be in protected form before any reaction is initiated. In such instances, removal of the protecting group may be the final step in a particular reaction. Suitable protecting groups for such functionality will be apparent to those skilled in the art. For specific details see Greene *et al*, "Protective Groups in Organic Synthesis", Wiley Interscience.

A process for preparing compounds of general formula (I) comprises acylating amine of formula B_2NH (II) with an acylating agent of formula $Z\text{-}X\text{-}(CH_2)_m\text{-}W\text{-}(CR^1R^2)_n\text{-}COY$ (III) wherein Z represents a suitable leaving group (e.g. a halogen such as chlorine), and Y is OH or NHOH or protected forms thereof such as OR^{10} (where R^{10} is a suitable protecting group such as benzyl or *tert*-butyl) or $NHOR^{11}$ (where R^{11} is a suitable protecting group such as benzyl, *tert*-butyl or tert-butyldimethylsilyl).

Acylating agents of formula (III) where m = 0 and X is SO_2, if not available commercially, may be prepared in a two-step process involving the sulfonation of an aromatic group of formula $W\text{-}(CR^1R^2)_n\text{-}COY$ (IV) to give a sulfonic acid $HO\text{-}SO_2\text{-}W\text{-}(CR^1R^2)_n\text{-}COY$ (V) followed by activation to (III). Many compounds of formula (IV) are available, or may be prepared by methods known to those skilled in the art.

Acylating agents of formula (III) where m = 1 and X is SO_2 may be prepared from compounds of formula $R^{12}S\text{-}CH_2\text{-}W\text{-}(CR^1R^2)_n\text{-}COY$ (VI) , where R^{12} is H or a suitable labile group such as acetyl, by treatment with chlorine in an appropriate solvent such as water at an appropriate temperature such as 0 °C. Acylating agents of formula (III) where X = SO may be prepared from compound (VI) by treatment with SO_2Cl_2 and acetic anhydride in an appropriate solvent such as dichloromethane at an appropriate temperature such as 0 °C.

Sulfanyl compounds of formula (VI) may be prepared readily by alkylation of a compound $R^{12}SH$ with an alkylating agent of the form $Z^{\wedge}\text{-}CH_2\text{-}W\text{-}(CR^1R^2)_n\text{-}COY$ (VII), where $Z^{\wedge}$ is a leaving group (e.g. a halogen such as bromine, or an alkylsulfonate ester such as methanesulfonate). Many compounds of the form (VII) are available commercially, or may be prepared by standard chemistry known to those skilled in the art from materials available commercially.

Amines of the structure depicted in formula (II) are commercially available or may be prepared by standard aromatic, heteroaromatic or other chemistry known to those skilled in the art, from commercially available materials.

Compounds of formula (I) may also be prepared by interconversion of other compounds of formula (I). Thus, for example, compound of formula (I) where $X=SO_2$ may be prepared from a compound of formula (I) where X=SO by oxidation with, for example sodium periodate and ruthenium chloride trihydrate in an appropriate solvent, for example acetonirtile-tetrachloromethane-water. Hydroxamic acids (Y=NHOH) of general

formula (I) may be prepared from carboxylic acids (Y=OH) of formula (I) using methods known to those skilled in the art.

Similarly, intermediates of any appropriate formula may be prepared by the interconversion of other compounds of the same formula. Thus, for example, a compound of formula (VI) where R^2 is not H may be prepared from a compound of formula (VI) where R^2 is H by reaction with a compound R^2Z (where Z is as defined above) in the presence of a strong base such as lithiumdiisopropylamide in an inert solvent such as tetrahydrofuran.

Any mixtures of final products or intermediates obtained can be separated on the basis of the physico-chemical differences of the constituents, in known manner, into the pure final products or intermediates, for example by chromatography, distillation, fractional crystallization, or by formation of a salt if appropriate or possible under the circumstances.

The compounds according to the invention exhibit *in vitro* inhibiting activities with respect to the stromelysins, collagenases and gelatinases. Compounds according to the invention may also exhibit *in vitro* inhibition of membrane shedding events known to be mediated by metalloproteinases, for example, α-APP, ACE, TGF-α, TNF-α, Fas ligand, TNFR-I, TNFR-II, CD30, Il-6R, CD43, CD44, CD16-I, CD16-II, Folate receptor, CD23, or IL-1RII.

The activity and selectivity of the compounds may be determined by use of the appropriate enzyme inhibition test, for example as described in Examples A-M of WO-A-9805635, by the assay for the inhibition of CD23 shedding described in PCT/GB98/03395, or by the following assay of TNF RI shedding.

The potency of the compounds of general formula (I) to act as inhibitors of the production of TNF RI is determined using the following procedure. A 100μM solution of the inhibitor being tested or dilutions thereof is incubated at 37° C in an atmosphere of 5% CO_2 with peripheral blood mononuclear cells (PBMC). PBMC are isolated from buffy coats by standard procedures using Ficoll. A 100μM solution of the inhibitor being tested or dilutions thereof is incubated for 22 hours at 37° C in an atmosphere of 5% CO_2 with 1 x 10^6/ml PBMC stimulated with LPS. The cells are centrifuged down and the supernatant is assayed for TNF RI using a commercially available ELISA kit (R & D Systems). The activity in the presence of 0.1mM inhibitor or dilutions thereof is compared

to activity in a control devoid of inhibitor and results reported as that inhib concentration effecting 50% inhibition of the production of TNF RI.

This invention also relates to a method of treatment for patients (including man and/or mammalian animals raised in the dairy, meat or fur industries or as pets) suffering from disorders or diseases which can be attributed to stromelysin as previously described, and more specifically, a method of treatment involving the administration of the matrix metalloproteinase inhibitors of formula (I) as the active constituents.

Accordingly, the compounds of formula (I) can be used among other things in the treatment of osteoarthritis and rheumatoid arthritis, and in diseases and indications resulting from the over-expression of these matrix metalloproteinases such as found in certain metastatic tumour cell lines.

As mentioned above, compounds of formula (I) are useful in human or veterinary medicine since they are active as inhibitors of TNF and MMPs. Accordingly in another aspect, this invention concerns:

a method of management (by which is meant treatment of prophylaxis) of disease or conditions mediated by TNF and/or MMPs in mammals, in particular in humans, which method comprises administering to the mammal an effective, amount of a compound of formula (I) above, or a pharmaceutically acceptable salt thereof; and

a compound of formula (I) for use in human or veterinary medicine, particularly in the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by TNF and/or MMPs; and

the use of a compound of formula (I) in the preparation of an agent for the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by TNF and/or MMPs.

The disease or conditions referred to above include inflammatory diseases, autoimmune diseases, cancer, cardiovascular diseases, diseases involving tissue breakdown such as rheumatoid arthritis, osteoarthritis, osteoporosis, neurodegeneration, Alzheimer's disease, stroke, vasculitis, Crohn's disease, ulcerative colitis, multiple sclerosis, periodontitis, gingivitis and those involving tissue breakdown such as bone resorption, haemorrhage, coagulation, acute phase response, cachexia and anorexia, acute infections, HIV infections, fever, shock states, graft versus host reactions, dermatological conditions, surgical wound healing, psoriasis, atopic dermatitis, epidermolysis bullosa, tumour growth,

angiogenesis and invasion by secondary metastases, ophthalmological disease, retinopathy, corneal ulceration, reperfusion injury, migraine, meningitis, asthma, rhinitis, allergic conjunctivitis, eczema, anaphylaxis, restenosis, congestive heart failure, endometriosis, atherosclerosis, endosclerosis and aspirin-independent anti-thrombosis.

Compounds of formula (I) may also be useful in the treatment of pelvic inflammatory disease (PID), age-related macular degeneration and cancer-induced bone resorption. Further, they can be used in the treatment of lung diseases, e.g. selected from cystic fibrosis, adult respiratory distress syndrome (ARDS), emphysema, bronchitis obliterans-organising pneumonia (BOOP), idiopathic pulmonary fibrosis (PIF), diffuse alveolar damage, pulmonary Langerhan's cell granulamatosis, pulmonary lymphangioleiomyomatosis (LAM) and chronic obstructive pulmonary disease (COPD).

For the treatment of rheumatoid arthritis, osteoarthritis, and in diseases and indications resulting from the over-expression of matrix metalloendoproteinases such as found in certain metastatic tumour cell lines or other diseases mediated by the matrix metalloendoproteinases or increased TNF production, the compounds of formula (I) may be administered orally, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats etc, the compounds of the invention are effective in the treatment of humans.

The pharmaceutical composition containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or

sodium phosphate; granulating and disintegrating agents, for example corn starch, alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the US Patents 4,256,108; 4,166,452; and 4,265,874, to form osmotic therapeutic tablets for control release.

Formulations for oral use may also be presented as hard gelatin capsules where in the active ingredient is mixed with an inert solid diluent, for example calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such a polyoxyethylene with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavouring agents may be added to provide a palatable oral preparation.

These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified, for example sweetening, flavouring and colouring agents may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally- occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soya bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavouring and colouring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be in a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of formula (I) may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary

temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc containing the compounds of Formula (I) are employed. For the purposes of this specification, topical application includes mouthwashes and gargles.

Dosage levels of the order of from about 0.05 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above- indicated conditions (about 2.5 mg to about 7 g per patient per day). For example, inflammation may be effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day (about 0.5 mg to about 3.5 g per patient per day).

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may vary from about 5 to about 95% of the total composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

CLAIMS

1. A compound of formula (I)

$$(B)_2N\text{-}X\text{-}(CH_2)_m\text{-}W\text{-}(CR^1R^2)_n\text{-}COY \qquad (I)$$

wherein

n = 0 or 1;

m = 0 or 1;

X is $S(O)_{1-2}$;

Y is OH or NHOH;

W is aryl or heteroaryl;

R^1 is H or a group (optionally substituted with R^3) selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, C_{1-6} alkyl-aryl, heteroaryl, C_{1-6} alkyl-heteroaryl, cycloalkyl, C_{1-6} alkyl-cycloalkyl, heterocycloalkyl and C_{1-6} alkyl-heterocycloalkyl; and

R^2 is H or C_{1-6} alkyl;

or CR^1R^2 is cycloalkyl or heterocycloalkyl optionally substituted with R^3 or a group (optionally substituted with R^3) selected from C_{1-6} alkyl, aryl, C_{1-6} alkyl-aryl, heteroaryl and C_{1-6} alkyl-heteroaryl;

R^3 is OR^7, COR^7, CO_2R^6, $CON(R^7)_2$, $N(R^7)_2$, NR^7COR^7, $NR^7CON(R^7)_2$, $NR^7CO_2R^8$, $NR^7SO_2R^8$, $S(O)_{0-2}R^8$, $SO_2N(R^7)_2$ or cycloimidyl (optionally substituted with R^4);

R^4 is C_{1-6} alkyl;

B is H or a group (optionally substituted with R^5) selected from C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl, C_{1-6} alkyl-aryl, heteroaryl, C_{1-6} alkyl-heteroaryl, cycloalkyl, C_{1-6} alkyl-cycloalkyl, heterocycloalkyl, C_{1-6} alkyl-heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl; and each instance of B may be the same or different;

or B-N-B is heterocycloalkyl optionally substituted with R^5 or $=NOR^5$;

R^5 is H, R^6 or a group (optionally substituted with R^6) selected from C_{1-6} alkyl, aryl, C_{1-6} alkyl-aryl, heteroaryl, C_{1-6} alkyl-heteroaryl, cycloalkyl, C_{1-6} alkyl-cycloalkyl, heterocycloalkyl and C_{1-6} alkyl-heterocycloalkyl;

R^6 is H or a group selected from $N(R^7)_2$, NR^7COR^7, $NR^7CON(R^7)_2$, $NR^7CO_2R^8$, $NR^7SO_2R^8$, OR^7, COR^7, CO_2R^4, $CON(R^7)_2$, $S(O)_{0-2}R^8$ and $SO_2N(R^7)_2$;

R^7 is H or a group selected from C_{1-6} alkyl, aryl, C_{1-6} alkyl-aryl, heteroaryl, C_{1-6} alkyl-heteroaryl, cycloalkyl, C_{1-6} alkyl-cycloalkyl, heterocycloalkyl and C_{1-6} alkyl-heterocycloalkyl, wherein said group is optionally substituted with R^8, COR^8, $SO_{0-2}R^8$, CO_2R^8, OR^8, $CONR^4R^8$, NR^4R^8, or $SO_2NR^4R^8$ and for each case of $N(R^7)_2$ the R^7 groups are the same or different or $N(R^7)_2$ is heterocycloalkyl optionally substituted with R^8, COR^8, $SO_{0-2}R^8$, CO_2R^8, OR^8, $CONR^4R^8$, NR^6R^8, or $SO_2NR^4R^8$; and

R^8 is C_{1-6} alkyl, aryl, C_{1-6} alkyl-aryl, heteroaryl or C_{1-6} alkyl-heteroaryl;

or a salt, solvate, hydrate, N-oxide, protected amino, protected carboxy or protected hydroxamic acid derivative thereof.

2. A compound of claim 1, wherein Y is NHOH.

3. A compound of claim 1 or claim 2, wherein B-N-B is optionally substituted heterocycloalkyl.

4. A compound of any preceding claim, wherein X is SO_2.

5. A compound of any preceding claim, which is in the form of a single enantiomer or diastereomer.

6. A pharmaceutical composition for use in therapy, comprising a compound as defined in any preceding claim, and a pharmaceutically-acceptable diluent or carrier.

7. Use of a compound according to any of claims 1 to 5, for the manufacture of a medicament for the treatment or prevention of a condition associated with matrix metalloproteinases or that is mediated by TNF α or enzymes involved in the shedding of *L*-selectin, CD23, the TNF receptors, IL-1 receptors or IL-6 receptors.

8. Use according to claim 7, wherein the condition is selected from cancer, inflammation and inflammatory diseases, tissue degeneration, periodontal disease, ophthalmological disease, dermatological disorders, fever, cardiovascular effects, haemorrhage, coagulation and acute phase response, cachexia, anorexia, acute infection, HIV infection, shock states, graft versus host reactions, autoimmune disease, reperfusion injury, meningitis, migraine and aspirin-independent anti-thrombosis.

9. Use according to claim 7, wherein the condition is selected from tumour growth, angiogenesis, tumour invasion and spread, metastases, malignant ascites and malignant pleural effusion.

10. Use according to claim 7, wherein the condition is selected from cerebral ischaemia, ischaemic heart disease, rheumatoid arthritis, osteoarthritis, osteoporosis, asthma, multiple sclerosis, neurodegeneration, Alzheimer's, atherosclerosis, stroke, vasculitis, Crohn's disease and ulcerative colitis.

11. Use according to claim 7, wherein the condition is selected from corneal ulceration, retinopathy and surgical wound healing.

12. Use according to claim 7, wherein the condition is selected from psoriasis, atopic dermatitis, chronic ulcers and epidermolysis bullosa.

13. Use according to claim 7, wherein the condition is selected from periodontitis and gingivitis.

14. Use according to claim 7, wherein the condition is selected from rhinitis, allergic conjunctivitis, eczema and anaphylaxis.

15. Use according to claim 7, wherein the condition is selected from restenosis, congestive heart failure, endometriosis, atherosclerosis and endosclerosis.

16. Use according to claim 7, wherein the condition is selected from pelvic inflammatory disease (PID), age-related macular degeneration and cancer-induced bone resorption.

17. Use according to claim 7, wherein the condition is a lung disease.

18. Use according to claim 17, wherein the condition is selected from cystic fibrosis adult respiratory distress syndrome (ARDS), emphysema, bronchitis obliterans-organising pneumonia (BOOP), idiopathic pulmonary fibrosis (PIF), diffuse alveolar damage, pulmonary Langerhan's cell granulamatosis, pulmonary lymphangioleiomyomatosis (LAM) and chronic obstructive pulmonary disease (COPD).

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